UNITED STATES DEPARTMENT F COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/722,659	09/27/96	BENNETT D	104385.140

HM11/0522

HOLLIE L BAKER
HALE AND DORR
1455 PENNSYLVANIA AVENUE NW
WASHINGTON DC 20004-1008

EXAMINER	
LUBET, M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/22/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/772,659	Applicant(s) Bennett et al.
	Examiner Lubet	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Mar 2, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-7* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

TC

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Group 1600 Art Unit 1644.

2. This office action is in response to Paper 6 filed March 2, 1998.

3. Examiner acknowledges the cancellation of claims 8-17 in the above mentioned Paper 6 Claims 1-7 are under examination.

4. The text of those section of Title 35, U.S.C. not included in this action can be found in a prior office action.

5. **(withdrawn in part)** Claims 1-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. (withdrawn) The term "decrease" in claim 1 and "decreases" in Claim 3 are relative terms which render these claims indefinite. The term "decrease" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.
--Applicant's response on pages 2- 3 of Paper 6 has been interpreted to mean that the terms should be interpreted broadly to mean any significant decrease in inflammation or detectable accumulation as compared with untreated or control patients.

B. (withdrawn) The term "inhibits" in claim 5 is a relative term which renders the claim indefinite. The term "inhibits" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.
--Applicant's response on pages 2- 3 of Paper 6 has been interpreted to mean that the terms should be interpreted broadly to mean any significant decrease in inflammation or detectable accumulation as compared with untreated or control patients.

C. (maintained) The term "overexpressed " in claim 6 is a relative term which renders the claim indefinite. The term "overexpressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would

not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.
--Applicant's response on pages 2- 3 of Paper 6 has been considered but does not help to define the metes and bounds of the terms "overexpressed." How does this term differ from "expressed"?

D.(withdrawn) In claim 1, it is unclear if the heparinase is administered directly to the site of inflammation, IE topically, or systemically, IE intravenously. Does " administration" encompass systemic and topical administration?
-- Applicant's response on page 3 of Paper 6 indicates that the heparinase enzymes can be administered either locally or systemically and the heparinase enzymes can be by infusion, injection or perfusion.

E. (maintained) In claims 1-7, it is unclear what an "heparinase enzyme" is. What enzymatic reaction does the heparinase mediate? Does the term encompass platelet heparitinase taught by Vlodavsky et al.(AB) (see page 116, in particular)? It is noted that "heparanase" is an alternative spelling for "heparinase."
--Applicant's response on page 3 has been considered but is not persuasive. Applicant does not address the issue as to whether the term "heparinase enzyme" encompasses platelet heparitinase taught by Vlodavsky. Is it Applicant's intent to claim a method of decreasing localized inflammatory responses by administering any enzyme which degrades heparin or heparin sulfate?
6.(Moot) Claim 16 provides for the use of heparinase , but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).
-- The rejection is moot because claim 16 has been canceled.

7. (maintained) Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to decrease inflammatory response in ischemic tissue, does not reasonably provide enablement for numerous inflammatory diseases or conditions disclosed on page 1, lines 25-35. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Reasons are set forth below

A. The effectiveness of treating inflammatory conditions such as organ transplantation, allograft rejection, rheumatoid arthritis, asthma, rhinitis and glomerulonephritis by administering heparinase *in vivo* is unknown.

Pharmaceutical therapies are unpredictable for the following reasons: (1) the peptide(s) or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to inherently short half-life of the peptide or protein; (2) the peptide(s) or protein may not reach the target area, i.e. the peptide(s) or protein may not be not be able to cross the mucosa or may be adsorbed by fluids, cells and tissues where the peptide(s) or protein has no effect, (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD. APP. & Inter. 1992).

Burnham (U)(AM. J. Hospt Pharm 51: 210, 1994) teach that use of therapeutic proteins is unpredictable because the proteins have poor stability and short half-lives *in vivo* and their repeated use leads to immunogenic response, leading to a vicious cycle of raising the dose, which enhances the immune reaction which increases clearance.

Therefore, in view of the nature of the invention, the state of the art, the amount of guidance present in the specification, and the breath of the claims, it would take undue experimentation to practice the claimed invention.

-- Applicant's response on pages 4-5 has been considered but is not persuasive. There is no data to indicate that the administration of heparinase enzymes is effective in treating chronic diseases such as arthritis, asthma, rhinitis and glomerulonephritis. Applicant's response that Applicant is not claiming a treatment for allograft per se but that the applicant is claiming a method of treating localized inflammatory response in a tissue following ischemic reperfusion injury is not persuasive because the claims are not limited to treating inflammation resulting form ischemic/reperfusion injury. The claim language encompasses treating localized inflammatory responses that may result from chronic diseases such as the ones cited above.

8. (maintained) Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogewerf et al. (W) (J. Biol. Chem 270:3268, February, 1995) or Gilat et al. (X)(J. Exp. Med. 181:1929, May, 1995), Vlodavsky et al (AA) (Invasion Metastasis 12: 112, 1991), Zimmerman et al. US 5,169,772 (issued Dec. 8, 1992) Fuks et al. US Patent 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991) and Sasisekharan et al. US Patent 5,567,417 (issued October 22, 1996 has priority to November 17, 1993) in view of Lider et al. (Y)(PNAS 92:5037, May 1995), Ratner et

al. (Invasion Metastasis 12:82, 1992) or Gilat et al (AA) (J. Immunol. 153:4899, 1994). The claims are directed to methods of treating localized inflammatory responses by administering heparinase enzymes. Claim 6 recites a limitation wherein the heparinase enzyme is overexpressed from a recombinant nucleotide sequence in Flavobacterium heparinum. Claim 7 recites a limitation wherein the heparinase enzyme is expressed from a recombinant nucleotide sequence in an organism in which it does not naturally occur.

A. Hoogewerf et al. teach a pharmaceutical composition comprising heparanase enzyme obtained from human platelets (see abstract and page 3269, in particular).

B. Gilat et al. teach pharmaceutical composition comprising heparanase enzyme obtained from human placenta (see pages 1929-1930, in particular).

C. Vlodavsky et al. teach a heparanase enzyme, heparitinase. The heparitinase enzyme taught by Vlodavsky et al. is encompassed by the claim language since the specification discloses on page 14, lines 19-33 that heparanase enzyme is an enzyme that degrades heparin.

D. The '772 Patent discloses heparinase enzymes expressed by *Flavobacteruim heparinum* and a method of producing heparinase enzyme recombinantly in an organism in which it does not naturally occur (see column 3, line 26 through column 6, line 16, and column 8 line 4 through column 10 and claims 1-2, in particular).

E. The '641 Patent discloses purified heparanase obtained from human SK-HEP-1 in a pharmaceutical composition (see column 12, line 59 through column 16, line 54 and claims 1-39, in particular). The '641 Patent further teaches that FGF is released by addition of heparanase to extracellular matrix (ECM) which promotes wound healing. The '641 Patent also discloses but does not exemplify that administration of heparanase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and peripheral ischaemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular).

F. The '417 Patent discloses pharmaceutical compositions for delivering an effective dose of heparinase (see column 8, line 29 through column 11, line 7 and Claims 1 in particular). The '417 Patent also discloses that the heparinase may be administered in composition comprising biodegradable polymeric matrices or liposomes (see Claims 4 and 8, column 16, lines 17-27, in particular). The '417 Patent discloses three heparin enzymes produced by Flavobacterium heparinum. The '417 Patent further discloses that Heparinases I and II inhibits both neovascularization *in vivo* and proliferation of capillary endothelial cells mediated by fibroblast growth factor in vitro. The '417 Patent also teaches that Heparinase II did not inhibit neovascularization *in vivo*, but is useful in the alteration of smooth muscle cell proliferation (see column 3, line 33 through column 4, line 39, in particular). The '417 Patent further discloses but does not exemplify the use of heparinase to treat disease in which neovascularization plays a

prominent role such as rheumatoid arthritis and eye diseases such as diabetic retinopathy, neovascular glaucoma, and inflammatory eye disease (see column 1, line 47 through column 2, line 25, in particular).

G. Hoogewerf et al., Gilat et al, , Vlodavsky et al. and the '772 Patent do not teach the use of the heparinase enzymes to treat inflammatory responses or that heparinase enzyme decreases accumulation of leukocytes or inhibits leukocyte extravasation. However, the limitations recited in Claims 2-5 are inherent properties of the heparinase enzymes.

Ratner et al. teach that heparanases digests heparin and heparin sulfate from endothelial cell surfaces and facilitates T cell movement through the basement membranes (see page 82, in particular).

Gilat et al.(AA) teach that heparanases degrades heparin from ECM which leads to the release of cytokines which leads to lymphocytes becoming mobile and migrating to adjacent sites of inflammation.

Lider et al teach that heparanase inhibits secretion of TNFα and that TNFα is a major mediator in T cell mediated inflammatory responses.

The '641 and '417 Patents disclose but do not exemplify administration of heparanases to treat localized inflammatory responses in a variety of diseases including cerebral and peripheral ischaemic disease, diabetes, systemic lupus, inflammatory eye disease and rheumatoid arthritis.

Therefore it would have been obvious to one with skill in the art to administer heparinase enzymes taught by Hoogewerf et al., Gilat et al., Vlodavsky et al., and the '772 , the '641 and the '417 Patents with the expectation that inflammatory responses would be decreased as taught by the '641 and '417 Patents and Lider et al.

-- Applicant's response on pages 5-7 have been carefully considered but is not persuasive.

The rejection set forth in section 21 of Paper 4 mailed Oct. 3,1 997 has been modified in response to Applicant's argument that Lider et al. does not teach the use of heparinase to treat DTH responses.

Applicant's response that DTH is not an inflammatory response because it is not within the definition of the term as defined in the specification is not persuasive. Page 1 of the specification defines an inflammatory response as a local response to cellular injury that is marked by capillary dilation, leukocytic infiltration, redness, heat and pain. Thus Applicant's definition of the inflammatory response encompasses inflammatory responses encompasses transplantation, diabetes, hypertension, cerebral and peripheral ischaemic disease, and diseases associated with

vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular). Applicant's argument that the references in combination do not teach the claimed invention is not persuasive. One with skill in the art would be motivated to administer heparinase to patients with the expectation that heparinase would degrade heparin at the cite of inflammation thus leading the T cell movement through the basement membranes for the reasons taught by Ratner et al. or inhibit TNF α secretion which would lead to a decrease in inflammation for the reasons taught by Lider et al.

9. (maintained) The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are provisionally rejected under the judicially created doctrine of obvious-type double patenting over claims 1-10 of copending Application No. 08/273,109.Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of 08/273,109 pertain to method of treating wounds by administering heparinase. Wound healing is a type of inflammatory response, since inflammatory cells, such as neutrophils, participate in wound healing and many of the "inflammatory cytokines" IE TNF-α are participate in wound healing.

--The rejection is maintained. Applicants have requested that the rejection be held in abeyance until allowable subject matter is indicated in the instant application and in 08/273,109.

10. Examiner believes that all pertinent arguments have been addressed.

11. No claim is allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973 The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet
May 15, 1998

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800